

mental design may underlie observed differences in sensitivity to detect neurotoxicity, possibly because of differences in biokinetics and exposure during sensitive windows of development. Fortunately, much effort is taking place in the scientific community to optimize experimental designs at different levels of biological complexity, including (developmental) neurobehavioral studies. Although a critical review on the impact of different experimental designs for *in vivo* (developmental) neurotoxicity studies would be very useful, it was beyond the scope of our review (Dingemans et al. 2011).

*The authors declare they have no actual or potential competing financial interests.*

**Milou M.L. Dingemans**  
**Martin van den Berg**  
**Remco H.S. Westerink**

Institute for Risk Assessment Sciences  
 Utrecht University  
 Utrecht, the Netherlands  
 E-mail: m.dingemans@uu.nl

## REFERENCES

- Alcock RE, Macgillivray BH, Busby JS. 2011. Understanding the mismatch between the demands of risk assessment and practice of scientists—the case of deca-BDE. *Environ Int* 37:216–225.
- Dingemans MML, van den Berg M, Westerink RHS. 2011. Neurotoxicity of brominated flame retardants: (in-)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environ Health Perspect* 119:900–907; doi:10.1289/ehp.1003035 [Online 18 January 2011].
- Eriksson P. 2008. Response to: Use of the pup as the statistical unit in developmental neurotoxicity studies: overlooked model or poor research design? [Letter]. *Toxicol Sci* 103:411–413.
- Gee JR, Moser VC. 2008. Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. *Neurotoxicol Teratol* 30:79–87.
- Hardy M, Stedeford T. 2008. Developmental neurotoxicity: when research succeeds through inappropriate statistics. *Neurotoxicology* 29:476.
- Williams AL, DeSesso JM. 2010. The potential of selected brominated flame retardants to affect neurological development. *J Toxicol Environ Health B Crit Rev* 13:411–448.
- Diez-Roux AV. 2002. A glossary for multilevel analysis. *J Epidemiol Community Health* 56(8):588–594.
- Jacob P, Kenigsberg Y, Zvonova I, Goulko G, Buglova E, Heidenreich WF, et al. 1999. Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. *Br J Cancer* 80(9):1461–1469.
- Robinson WS. 1950. Ecological correlations and the behavior of individuals. *Am Sociol Rev* 15(3):351–357.
- Subramanian SV, Jones K, Kaddour A, Krieger N. 2009. Revisiting Robinson: the perils of individualistic and ecological fallacy. *Int J Epidemiol* 38(2):342–360.

## Three Criteria for Ecological Fallacy

doi:10.1289/ehp.1103768

In a large cohort study published in *Environmental Health Perspectives*, Brenner et al. (2011) confirmed previous results on I-131 exposure and thyroid cancer among

a Ukrainian population. According to the authors, one motivation to study this association was based on evidence from ecological studies (Jacob et al. 1999) with two methodological limitations: use of grouped doses and poor control of confounding. With these new findings, evidence from ecological, case-control, and cohort studies are consistent; thus, an interesting question is whether there was an ecological fallacy.

Although ecological studies are important to epidemiology (especially in environmental and social epidemiology), public health practitioners seem afraid of ecological studies. It is a common practice to assume the presence of ecological fallacy (Robinson 1950) and low-level validity when analyzing an ecological study. Most epidemiologists prefer an exclusive individualistic approach, although the importance of a multilevel causal approach is widely recognized (Diez-Roux 2002). In this sense, some authors suggest that it is as important to recognize the presence of ecological fallacy as to recognize psychologicistic or individualistic fallacy (Subramanian et al. 2009) (Figure 1).

Thus, it is necessary to have clear guidelines on when there is or not an ecological fallacy. In this sense, I propose three criteria for the identification of ecological fallacy; all three of these should be present to confirm its existence:

- Results must be obtained with ecological (population) data.
- Data must be inferred to individuals. One use of ecological studies is to explore individual-level association when individual data are not available. When the focus of the study was contextual or based on population effects and there is no inference to individuals, ecological fallacy is not possible. When only the first two criteria are present—which is insufficient to affirm ecological fallacy—it is appropriate to acknowledge that there is a possible relationship and that further study is required.
- Results obtained with individual data are contradictory.

Only when empirical data are available is it possible to confirm that an ecological fallacy is present.

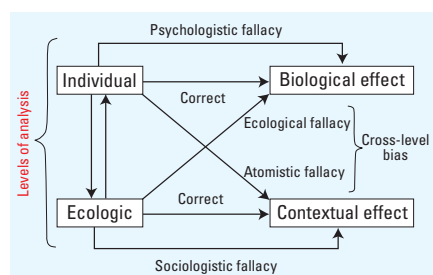
*The author declares that he has no competing financial interests.*

**Alvaro J. Idrovo**

Center for Health Systems Research  
 National Institute of Public Health  
 Cuernavaca, Morelos, Mexico  
 E-mail: javier.idrovo@insp.mx

## REFERENCES

- Brenner AV, Tronko MD, Hatch M, Bogdanova TI, Olynyk VA, Lubin JH, et al. 2011. I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. *Environ Health Perspect* 119:933–939; doi:10.1289/ehp.1002674 [Online 17 March 2011].



**Figure 1.** Levels of analysis in epidemiologic studies and potential fallacies during causal inference.

## Carbon Black

doi:10.1289/ehp.1103444

In “Research Recommendations for Selected IARC-Classified Agents,” Ward et al. (2010) identified research gaps for 20 occupational agents “based on evidence of widespread human exposures and potential carcinogenicity in animals or humans.” (Ward et al. 2010) For carbon black, the authors suggested that

Research needs include updating epidemiology cohorts with data on work histories and exposures in relation to particle size and surface area, and recruitment of additional carbon black facilities. The relationship between occupational exposure to carbon black and validated biomarkers of oxidative stress should be examined and exposure-response relationships in humans and rodents quantified, including the role of particle size.

Ward et al. (2010) referred to a study of British carbon black workers in which carbon black was suggested as a possible “late stage carcinogen” (Sorahan and Harrington 2007). In that study, Sorahan and Harrington (2007) called for similar analyses of other carbon black cohorts (i.e., evaluating the possibility of carbon black acting as a late stage carcinogen via the concept of “lugging,” which considers only recent exposures and not historical exposures). In response to suggestions made by Sorahan and Harrington, we conducted such analyses on a large German carbon black cohort (Morfeld and McCunney 2007, 2009). We were unable to reproduce the results of the British analysis, despite the elevation noted in lung cancer among German cohort workers, thus providing no support for the late stage-lugging hypothesis. Results of a detailed analysis of the German cohort using Bayesian methodology showed smoking and exposure to occupational carcinogens prior to work at the carbon black plant as confounders probably responsible for the lung cancer excess (Morfeld and McCunney 2010).

Ward et al. (2010) called for enhanced exposure-response assessments in humans. Currently, a dose-response exposure analysis is under way on the U.S. carbon black cohort (> 5,000 production workers). An earlier evaluation of this cohort showed no increase in any type of cancer (Dell et al. 2006).

Ward et al. (2010) recommended that “the relationship between occupational exposure to carbon black and validated biomarkers of oxidative stress should be examined.” Despite the appeal of biomarkers of oxidative stress in pinpointing inflammatory changes associated with malignant and nonmalignant illnesses, such markers are nonspecific, not well validated, and appear not “ready for prime time,” as noted in a recent symposium on nanotoxicology (Fischman et al. 2011).

A meta-analysis of all three major carbon black cohorts (United States, United Kingdom, and Germany) to assess risk of heart disease is also under way. In a recent position paper, Brook et al. (2004) noted that particle exposure may play a role in the development of heart disease.

Ward et al. (2010) suggested evaluating carbon black particle size and surface area. However, the physical and chemical properties of untreated manufactured carbon blacks are distinctly different from ubiquitous carbon core particulates in both occupational and ambient atmospheres (Kuhlbusch and Fissan 2006). Approximately 90% of manufactured carbon black is used for tire and automotive rubber products. In products, such as toners, plastics, and surface coatings, carbon black is matrix-bound, and not an exposure risk to end-users. Care should be taken when applying quantitative models that claim to address the particle size and surface area topics (Tomenson and Morfeld 2010).

*The authors serve as scientific advisors to the International Carbon Black Association (ICBA), a scientific, non-profit corporation originally founded in 1977, with the purpose of sponsoring, conducting, and participating in investigations, research, and analyses relating to the health, safety, and environmental aspects of the production and use of carbon black. This manuscript was neither influenced by the ICBA nor by any company funding the ICBA, nor does it present any view or opinion of the ICBA or of the companies. H.M. is president of Muranko and Associates, a consulting company that provides industrial hygiene and safety services and serves as expert witness in industrial safety cases.*

**Robert J. McCunney**

Massachusetts Institute of Technology  
Cambridge, MA  
E-mail: mccunney@MIT.EDU

**Peter Morfeld**

Institute for Occupational Medicine  
at Cologne University  
Cologne, Germany

**Len Levy**

Emeritus Professor  
Institute of Environment and Health  
Cranfield University  
Cranfield, Bedfordshire, United Kingdom

**Henry Muranko**

Muranko and Associates  
Scottsdale, Arizona

*The Scientific Advisory Group of the International Carbon Black Association (ICBA) gave helpful comments on an earlier version of this letter.*

## REFERENCES

- Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. 2004. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 109(21):2655–2671.
- Dell LD, Mundt KA, Luippold RS, Nunes AP, Cohen L, Burch MT, et al. 2006. A cohort mortality study of employees in the U.S. carbon black industry. *J Occup Environ Med* 48(12):1219–1229.
- Fischman M, Storey E, McCunney RJ, Kosnett M. 2011. National Institute for Occupational Safety and Health Nanomaterials and Worker Health Conference—medical surveillance session summary report. *J Occup Med* 53(6 suppl):S35–S37.
- Kuhlbusch TA, Fissan H. 2006. Particle characteristics in the reactor and pelletizing areas of carbon black production. *J Occup Environ Hyg* 3(10):558–567.
- Morfeld P, McCunney RJ. 2007. Carbon black and lung cancer: testing a new exposure metric in a German cohort. *Am J Ind Med* 50(8):565–567.
- Morfeld P, McCunney RJ. 2009. Carbon black and lung cancer—testing a novel exposure metric by multi-model inference. *Am J Ind Med* 52(11):890–899.
- Morfeld P, McCunney R. 2010. Bayesian bias adjustments of the lung cancer SMR in a cohort of German carbon black production workers. *J Occup Med Toxicol* 5:23; doi:10.1186/1745-6673-5-23 [11 August 2010].
- Sorahan T, Harrington JM. 2007. A “lugged” analysis of lung cancer risks in UK carbon black production workers, 1951–2004. *Am J Ind Med* 50(8):555–564.
- Tomenson JA, Morfeld P. 2010. Multiple errors made by authors result in a huge overestimation of potential exposure to particles in the size range 10–30 nm in TiO<sub>2</sub> nanoparticle production facilities [Letter]. *J Hazard Mater* 183:954–955.
- Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreon T, et al. 2010. Research recommendations for selected IARC-classified agents. *Environ Health Perspect* 118:1355–1362.

## Carbon Black: Kuempel et al. Respond

doi:10.1289/ehp.1103444R

We appreciate the comments and additional information from McCunney et al. We are pleased to learn of the new epidemiological studies that are under way in the U.S. and E.U. carbon black cohorts. These studies may provide the opportunity to fill some of the research gaps discussed in our review (Ward et al. 2010). As mentioned by McCunney et al. in their letter, we recommend the collection of particle size–specific and quantitative exposure data, and the recruitment of additional facilities (Ward et al.). Studies in animals have shown relationships between the particle surface area dose of poorly soluble particles (including carbon black) in the lungs and biomarkers of oxidative stress and inflammation in rats and mice (Elder et al. 2005; Sager and Castranova 2009; Stoeger et al. 2006) and lung tumors in rats (Driscoll 1996; Heinrich et al. 1995; Nikula et al. 1995). Although these relationships

with particle surface area dose have not been reported in human studies, exposure to carbon black by particle mass has been associated with respiratory effects including lung function decrements in workers (Gardiner et al. 2001).

Concerning biomarkers of oxidative stress, we think the epidemiology studies under way may provide an opportunity to investigate and test hypotheses about possible biomarkers of exposure and response to carbon black. As we discussed in our paper (Ward et al. 2010), although oxidative stress has been invoked as a mechanism in the carcinogenicity of a number of agents (including particles such as carbon black), methodological challenges to the validation of oxidative stress biomarker assays remain. To facilitate this process, guidelines have been developed to standardize the collection and measurement of oxidative stress biomarkers in humans (American Thoracic Society 1999; Horváth et al. 2005).

We look forward to further reports from the carbon black mortality studies, including exposure–response analyses, which could help fill important occupational health research gaps. Well-conducted epidemiologic studies will be particularly critical to inform carcinogen classification and risk assessment processes.

*The findings and conclusions in this letter are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health, the University of Birmingham, the U.S. Environmental Protection Agency, the International Agency for Research on Cancer, or the American Cancer Society Inc.*

*The authors declare they have no actual or potential competing financial interests.*

**Eileen D. Kuempel**

**Paul A. Schulte**

National Institute for Occupational Safety and Health  
Cincinnati, Ohio  
E-mail: ekuempel@cdc.gov

**Thomas Sorahan**

Institute of Occupational and Environmental Medicine  
University of Birmingham  
Birmingham, United Kingdom

**Jane Caldwell**

U.S. Environmental Protection Agency  
Research Triangle Park, North Carolina

**Kurt Straif**

International Agency for Research on Cancer  
Lyon, France

**Elizabeth Ward**

American Cancer Society, Inc.  
Atlanta, Georgia